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In This Issue

Insulin Detemir

Indications

Insulin detemir is indicated for once- or twice-daily subcutaneous (subQ) administration in the treatment of adult patients with type 1 or 2 diabetes mellitus (DM) who require basal (long-acting) insulin for the control of hyperglycemia.[1]

Clinical Pharmacology

Insulin detemir (rDNA origin) (Lys^{B29}-tetradecanoyl, des-(B30) human insulin; NN304) is a neutral, soluble, insulin preparation in which the B29 lysine residue has been covalently bound to a 14-carbon fatty acid.[2–4] Insulin detemir is composed of four molecules of insulin in an asymmetric unit, plus four zinc ions, four chloride ions, four phenol molecules, four fatty acid side chains, and 153 water molecules. The four insulin molecules aggregate to form four dimers. The presence of zinc and phenol drives the formation of hexamers similar to those that occur with natural human insulin. The fatty acid side chains contribute to hexamer aggregation, which may help to delay hexamer dissociation and absorption. In the monomeric form, the fatty acid side chains are available on the surface to bind to albumin.[2-4] The fatty acid side chains primarily bind albumin via albumin domain III and more weakly via albumin domain I.[5] Insulin detemir is more than 98% bound to albumin in the plasma and more than 96% bound in the interstitial fluid.[6] Only the free insulin detemir is available to cross the endothelial barrier.[7]

The fatty acid extension facilitates the compound's ability to reservedly bind to albumin in the plasma, thereby prolonging the activity of insulin detemir by delaying its appearance in the interstitial fluid and delaying its action at insulin-sensitive tissues.[2–4]

The plasma elimination of insulin detemir is reduced to 10% of insulin, and the transendothelial transport of insulin detemir is reduced to 7% of regular insulin.[6] Serum insulin concentrations are increased significantly with insulin detemir, while insulin levels in the interstitial fluid are reduced to less than 10% of serum values. In contrast, human insulin levels in the interstitial fluid are 30 to 60% of those achieved in the serum.[4]

Although reduced transport appears to occur, transcapillary transport of insulin detemir in the skeletal muscle occurs via nonsaturable passive diffusion, the same transport mechanism thought to be responsible for the transport of regular human and porcine insulin.[4,8–10] The presence of supraphysiologic concentrations of human insulin do not interfere with insulin detemir transport.[10]

Compared with human insulin, insulin detemir has reduced receptor affinities and is not as effective on a molar basis as human insulin.[11,12] The lipophilicity and albumin binding of insulin detemir complicate receptor binding assays with this agent. Limited data suggest that the insulin receptor affinity of insulin detemir is 18 to 46% of that of human insulin. In contrast, the insulin receptor affinity of insulin glargine is 86%. Insulin detemir also has reduced metabolic potency, insulin-like growth factor 1 (IGF-1) receptor affinity, and mitogenic potency compared with human insulin.[11]

The time-action profile of insulin detemir 0.15, 0.3, and 0.6 units/kg administered subQ have been compared with that of NPH insulin 0.3 units/kg administered subQ in 11

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healthy volunteers. Peak insulin detemir concentrations were reached after 4 to 6 hours. A pronounced peak in metabolic effect was not observed with insulin detemir, in contrast with NPH insulin. Insulin detemir also demonstrated a slower onset of action.[7] In a similar study, insulin detemir 0.3 and 0.6 units/kg were also compared with NPH insulin 0.3 and 0.6 units/kg and placebo in 10 healthy volunteers. NPH insulin was more active at these doses than the equal doses of insulin detemir. As in the other study, insulin detemir was associated with a flatter activity profile.[12] A similar crossover study was also conducted comparing single doses of insulin detemir (0.1, 0.2, 0.4, 0.8, and 1.6 units/kg) with NPH insulin (0.3 units/kg) administered subQ in 12 patients with type 1 diabetes. While NPH insulin demonstrated peak activity around 6 to 8 hours, a flatter glucose infusion rate profile was observed for insulin detemir. The duration of action for the insulin detemir 0.4 unit/kg dose was 20 hours, ranging from 5.7 hours with the 0.1 unit/kg dose to 23.2 hours with the 1.6 unit/kg dose.[13,14] In another study enrolling six patients with type 1 diabetes, the peak action of insulin detemir was observed at 600 to 660 minutes after subQ injection.[15]

The within-subject variability in the pharmacodynamics of insulin detemir has been compared with that of insulin glargine and NPH insulin in a randomized, double-blind study enrolling 54 subjects with type 1 diabetes. All patients received a single subQ dose of 0.4 unit/kg of insulin detemir, insulin glargine, or NPH insulin on four separate occasions, with monitoring of the glucose infusion rate necessary to maintain a target blood glucose level of 100 mg/dL. Insulin detemir exhibited less within-subject variability as assessed by the coefficient of variation for the pharmacodynamic end points studied. For the area under the glucose infusion rate profile from time 0 to 12 hours, the coefficient of variation was 27% for insulin detemir, compared with 46% for insulin glargine and 59% for NPH insulin ($P < 0.001$). For the area under the glucose infusion rate profile from time 0 to 24 hours, the coefficient of variation was 27% for insulin detemir, compared with 48% for insulin glargine and 68% for NPH insulin ($P < 0.001$). For the peak glucose infusion rate, the coefficient of variation was 23% for insulin detemir, compared with 36% for insulin glargine and 46% for NPH insulin ($P < 0.001$).[16] Insulin detemir also exhibited less total variability in pharmacokinetics, compared with NPH insulin in a study enrolling children, adolescents, and adults.[17]

Pharmacokinetics

Insulin detemir is absorbed following subQ administration, but slowly transported to the peripheral tissue.[7] Peak plasma concentrations occur within 3 to 8 hours, then decline to baseline within 24 hours.[1,7,12,14] Maximal metabolic effect occurs within 6 to 11 hours after injection.[1,7,12] Absolute bioavailability is approximately 60%.[1] More than 98% of the insulin detemir in the bloodstream is bound to albumin.[1] The half-life of insulin detemir is 5 to 7 hours.[1,12] The key pharmacokinetic/ pharmacodynamic parameters of insulin detemir, insulin glargine, and NPH insulin are compared (in Table 1.)

Table 1. Key Pharmacokinetic/Pharmacodynamic Parameters of Insulin Detemir, Insulin Glargine, and NPH Insulin[1,18,19]

Insulin	Peak[a]	Duration
Insulin detemir	3 to 8 hr	5.7 to 23.2 hr
Insulin glargine	5 hr	10.8 to > 24 hr
NPH insulin	4 to 12 hr	Up to 24 hr

[a]Insulin detemir and insulin glargine are characterized by a relatively flat ("peakless") concentration/time profile.

The pharmacokinetics of insulin detemir are similar in children 6 to 12 years of age and adolescents 13 to 17 years of age, as in adults. In children, the area under the curve (AUC) was increased 10%, and the peak concentration was increased 24%, compared with adults. No difference in the pharmacokinetics was observed in the adolescents compared with adults.[1,17] In elderly subjects, the AUC was increased up to 35%, compared with younger adults.[1] Insulin detemir pharmacokinetics were also not influenced by race (white, Japanese, black, and Hispanic or Latino subjects).[1,20,21]

The pharmacokinetics of insulin detemir did not differ in subjects with moderate-to-severe renal impairment, compared with healthy subjects. In patients with hepatic impairment, clearance increased with increasing degrees of hepatic impairment but clinically important differences were not observed. Insulin detemir doses should be titrated to individual response in all patients, regardless of renal or hepatic function.[1,22]

Comparative Efficacy

The majority of these studies compared insulin detemir with NPH insulin. None of these studies compared insulin detemir with insulin glargine.

Type 1 Diabetes

Insulin detemir and NPH insulin were compared in a 6- month, open-label study enrolling 747 patients with type 1 diabetes. Patients were randomized 2:1 to therapy with insulin detemir or NPH insulin as basal insulin in conjunction with regular human insulin as bolus insulin. At baseline, the mean age was 40.5 years, mean duration of diabetes was 16.9 years, mean BMI was 25.2 kg/m^2, and mean glycosylated hemoglobin (HbA1C) was 8.35%. After 6 months, glycemic control was similar (mean difference in HbA_{1C} [insulin detemir – NPH], –0.12% [95% confidence interval (CI) – 0.25, 0.02]). Fasting plasma glucose levels were lower in patients treated with insulin detemir (–1.16 mmol/L; $P = 0.001$). Within-subject variability in self-monitored blood glucose values were lower with insulin detemir (standard deviation [SD], 2.82 vs 3.6 mmol/L; $P < 0.001$). The overall risk of hypoglycemia was similar in the two groups, although nocturnal hypoglycemia risk was 26% lower in patients receiving insulin detemir ($P = 0.003$). Patients lost a mean 0.23 kg in the insulin detemir group, but gained a mean 0.31 kg in the NPH group after 6 months of therapy (baseline adjusted mean difference, 0.54 kg; $P = 0.024$).[23,24]

Insulin detemir and NPH insulin were also compared in a 6-month, open-label study enrolling 447 patients with type 1 diabetes. Patients were randomized 2:1 to therapy with insulin detemir (301 patients) or NPH insulin (141 patients) as basal insulin in conjunction with insulin aspart as bolus insulin. At baseline, the mean age was 39.9 years, mean duration of diabetes was 16.8 years, mean BMI was 24.6 kg/m^2, and mean HbA1C was 8.1%. After 6 months, glycemic control was similar (mean HbA_{1C}, 7.6% with insulin detemir, and 7.64% with NPH insulin). Fasting plasma glucose levels were slightly lower in patients treated with insulin detemir (–0.76 mmol/L; $P = 0.097$). Within-subject variation in self-monitored fasting blood glucose was less in the insulin detemir group (SD, 3.37 vs 3.78 mmol/L; $P < 0.001$). The overall risk of hypoglycemia was 22% lower in the insulin detemir group (95% CI, 3 to 38%; $P < 0.05$) and nocturnal hypoglycemia risk was 34% lower in patients receiving insulin detemir (95% CI, 13 to 50%; $P < 0.005$). Baseline adjusted body weight was also lower in the insulin detemir group ($P < 0.001$), with patients in the insulin detemir group exhibiting a 0.2 kg weight loss compared with a 0.7 kg weight gain in the NPH group.[25–27]

Insulin detemir and NPH insulin were also compared in a randomized, open-label, 16-week study enrolling 408 patients with type 1 diabetes. Patients received insulin detemir or NPH insulin twice daily in conjunction with premeal insulin aspart. Insulin detemir was administered either before breakfast and at bedtime, or at a 12-hour interval, with results with each regimen compared with those of NPH insulin administered before breakfast and at bedtime. Fasting plasma glucose was lower with both insulin detemir regimens compared with NPH insulin (12- hour regimen: –1.5 mmol/L; 95% CI, –2.51 to –0.48; $P = 0.004$; breakfast-bedtime regimen: –2.3 mmol/L; 95% CI, –3.32 to –1.29; $P < 0.001$). Self-monitored pre-breakfast plasma glucose was also lower in the insulin detemir groups ($P = 0.006$ and $P = 0.004$). Although HbA_{1C} did not differ between each insulin detemir group and the NPH group, it was lower in the combined insulin detemir group (mean difference, –0.18%; 95% CI, –0.34 to –0.02; $P = 0.027$). Within-subject variability in self-monitored prebreakfast plasma glucose was lower in both insulin detemir groups ($P < 0.001$). No weight change was observed in either insulin detemir group, while weight gain was observed with NPH. Risk of nocturnal hypoglycemia was reduced 53% with the breakfast-bedtime regimen of insulin detemir ($P < 0.001$).[1,28]

Another randomized, openlabel study compared a basal-bolus regimen with insulin detemir and insulin aspart with a regimen of NPH insulin and regular human insulin in 595 patients with type 1 diabetes. After 18 weeks, HbA_{1C} declined to 7.88% in the insulin detemir group and 8.11% in the NPH group (mean difference, –0.22%; 95% CI, –0.34 to –0.1; $P < 0.001$). HbA_{1C} declined 0.5% in the insulin detemir/insulin aspart group and 0.28% in the NPH/regular insulin group. Lower postprandial glucose levels were observed in the insulin detemir/ insulin aspart group. Within-subject variability in plasma glucose was also lower with the insulin detemir/insulin aspart regimen (SD, 2.88 vs 3.12 mmol/L; $P < 0.001$). A 1 kg weight loss was observed in the insulin detemir/ insulin aspart group, compared with no change in the NPH/regular insulin group ($P < 0.001$). Risk of hypoglycemia was reduced 21% overall ($P = 0.036$) and 55% at night ($P < 0.001$) with insulin detemir/insulin aspart compared with the NPH/regular insulin regimen.[29]

A regimen of insulin detemir plus insulin aspart was also compared with a regimen of NPH insulin plus insulin aspart in a randomized, open-label, 26-week study enrolling 347 children and adolescents (mean age, 11.9 y). Insulin detemir and NPH insulin were administered once or twice daily according to the patient's prestudy regimen. Mean baseline HbA_{1C} was 8.8%, declining by 0.8% across the study population. HbA_{1C} improvement did not differ between study groups (mean difference, 0.09%; 95% CI, –0.12 to 0.29). Mean fasting plasma glucose was lower with insulin detemir (8.44 vs 9.58 mmol/L; $P = 0.022$). Within-subject variation in fasting plasma glucose was lower with insulin detemir (SD, 3.32 vs 4.29 mmol/L; $P < 0.001$). The overall shape of the glucose profile and mean nocturnal plasma glucose were similar with both insulins. Overall risk of hypoglycemia did not differ between the groups; however, the risk of nocturnal hypoglycemia was reduced 36% ($P = 0.011$) with the insulin detemir therapy. Baseline-adjusted BMI was also lower in the insulin detemir group (19.3 vs 19.8 kg/m^2; $P < 0.001$) after 26 weeks.[30]

Insulin detemir was compared with NPH insulin in an open-label, 12-month extension study originally enrolling 460 patients with type 1 diabetes treated with a basal-bolus regimen. Basal insulin was administered as a twice-daily injection. At baseline, the mean age was 39.2 years, mean duration of diabetes was 14.7 years, mean BMI was 25.3 kg/m^2, and mean HbA_{1C} was 7.6%. During the first 6 months, patients were randomized to therapy with insulin detemir or NPH insulin. Both agents maintained similar glycemic control as measured by HbA_{1C}, 9-point blood glucose profiles, and fasting plasma glucose. The incidence of hypoglycemia was comparable in the two groups. Of the 421 patients completing the original 6- month study, 288 patients (68%) continued their assigned treatment in the extension phase (154 patients receiving insulin detemir and 134 patients receiving NPH insulin). The 12-month study was completed by 252 patients (134 receiving insulin detemir and 118 receiving NPH insulin). Glycemic control was similar at 12 months. HbA_{1C} was 7.88% in the insulin detemir group and 7.78% in the NPH insulin group, and these were maintained near baseline levels throughout the study. Fasting plasma glucose and 9-point blood glucose profiles were also similar. Patients in the insulin detemir group lost 0.3 kg, while those in the NPH insulin group gained 1.4 kg (difference at 12 months, 1.7 kg; $P = 0.002$). A trend towards less nocturnal hypoglycemia was observed in the insulin detemir group (relative risk detemir/NPH, 0.71; $P = 0.067$).[31–33]

Insulin detemir was also compared with NPH insulin in another open-label, 12-month extension study enrolling 315 patients with type 1 diabetes treated with a basal-bolus regimen. The mean baseline HbA_{1C} was 8.13% in both groups. The study consisted of a 6-month randomized comparison period followed by a 6-month extension period. Patients were originally randomized 2:1 to twicedaily administration of insulin detemir or NPH insulin as a basal regimen in addition to insulin aspart bolus insulin. Of those completing the original 6-month study, 315 patients (74%) continued their assigned treatment in the extension phase (216 patients receiving insulin detemir and 99 patients receiving NPH insulin). The 12-month study was completed by 308 patients (212 receiving insulin detemir and 96 receiving NPH insulin). Glycemic control was similar in both groups at 12 months. HbA_{1C} was 7.53% in the insulin detemir group and 7.59% in the NPH insulin group. Fasting plasma glucose and 9-point blood glucose profiles were also similar. Baselineadjusted mean body weight after 12 months was lower in the insulin detemir group (71.2 vs 72.7 kg; $P < 0.001$); insulin detemir-treated patients lost an average of 0.1 kg, while those in the NPH group gained an average of 1.2 kg. The risk of nocturnal hypoglycemia was 32% lower in the insulin detemir group ($P = 0.02$). The overall risk of hypoglycemia did not differ.[34,35]

Insulin detemir was compared with NPH insulin in an open crossover study enrolling 59 patients with type 1 diabetes previously treated with a basal-bolus regimen including once-daily NPH insulin. Following a 2-week run-in period on a basal-bolus regimen, including NPH insulin once daily, patients completed two 6-week periods of optimized basal-bolus therapy with once-daily insulin detemir and NPH insulin. Mean dose requirements for insulin detemir were 2.35 times higher than those of NPH (95% CI, 2.22 to 2.48). The mean daily NPH dose was 0.28 units/kg, while that of insulin detemir was 0.67 units/kg. The mean daily dose of meal-related insulin remained constant (approximately 0.45 units/kg). The AUC for serum glucose for the overnight time period (23:00 to 08:00) did not differ between the two therapies; however, serum glucose was higher with insulin detemir until 02:00, representing a slower onset of action. Less intersubject variation in fasting blood glucose over the last 4 days of the study period was observed during insulin detemir therapy ($P < 0.001$). During the last week of treatment, hypoglycemia occurred less often during insulin detemir therapy (60%) than NPH therapy (77%; $P = 0.049$).[36]

In a Markov analysis projecting results from a meta-analysis of results from four studies comparing insulin detemir and NPH insulin in patients with type 1 diabetes, short-term improvements in HbA_{1C}, risk of hypoglycemia, and body weight changes were projected in the United Kingdom health care setting to result in fewer diabetes-related complications, an increase in quality-adjusted life expectancy of 0.09 years, increased total lifetime costs/patient of £1,707 (British pound sterling), and an incremental cost-effectiveness ratio of £19,285 per quality-adjusted life-year (QALY) gained.[37] In a similar cost-effectiveness analysis utilizing the same Center for Outcomes Research (CORE) Diabetes Model, Markov simulation applied with a UK National Health Service perspective projected an improvement in life expectancy (0.18 life-years gained) and quality-adjusted life expectancy (0.4 QALY gained) with insulin detemir plus insulin aspart, compared with NPH insulin plus insulin aspart. Lifetime costs were projected to be £2,747 higher with the insulin detemir regimen, leading to an incremental cost-effectiveness ratio of £15,261 per life year gained and £6,868 per QALY.[38] Another Markov-based cost-effectiveness model from the UK perspective projected an increase in life expectancy of 0.13 life-years gained and a 0.122 QALY gain with insulin detemir plus insulin aspart, compared with NPH insulin plus insulin aspart. Results of this assessment were projected to result in a £1,928 higher per patient lifetime costs and an incremental cost-effectiveness ratio of £15,246 per life-year gained and £15,803 per QALY.[39] Similar cost-effectiveness assessments have not been published examining insulin detemir in comparison with NPH insulin in the United States health care setting.

Type 2 Diabetes

Insulin detemir was also compared with NPH insulin in an open-label study enrolling 58 patients with type 2 diabetes treated with either NPH insulin or premixed insulin. During the first 2 weeks, patients continued their usual regimen of NPH insulin (30 patients) or premixed insulin (28 patients) once or twice daily. During the second period, lasting up to 5 weeks, patients previously on NPH were switched to insulin detemir and patients previously receiving premixed insulin were switched to insulin detemir plus human insulin. The dose of insulin detemir was adjusted to maintain blood glucose levels comparable with those prior to the switch. Comparable blood glucose levels were achieved after the switch. The mean ratio between molar doses of insulin detemir and NPH was 4.06 (95% CI, 3.23 to 5.11) for the NPH group and 3.6 (95% CI, 3.19 to 4.07) for the premixed insulin group. This study demonstrated that comparable blood glucose control could be achieved when approximately four times higher molar doses of insulin detemir were used in place of NPH insulin.[40]

A basal-bolus regimen of insulin detemir plus insulin aspart was compared with a regimen of NPH insulin and regular human insulin in an open-label, randomized study enrolling 395 patients with type 2 diabetes previously treated with a basal insulin regimen. Mean baseline HbA^{1C} was 8.16% in the insulin detemir group and 8.08% in the NPH group. At 22 weeks, HbA_{1C} was reduced by 0.65% from baseline with the insulin detemir regimen and by 0.58% from baseline with the NPH regimen to levels of 7.46% and 7.52%, respectively. Patients treated with the insulin detemir/insulin aspart regimen exhibited less variation in self-measured fasting plasma glucose (SD, 1.2 vs 1.54 mmol/L; $P < 0.001$) and less body weight gain (0.51 vs 1.13 kg; $P = 0.038$), although the weight gain from baseline was significant in both groups ($P < 0.02$ for insulin detemir/insulin aspart and $P < 0.001$ for NPH/regular). At 22-weeks, 31%

of patients in the insulin detemir group and 36% in the NPH group received basal insulin once daily; the rest received basal insulin twice daily.[41]

Another open-label randomized study compared a regimen of insulin detemir plus insulin aspart with a regimen of NPH insulin plus insulin aspart in 505 patients with type 2 diabetes previously treated with insulin therapy. Mean baseline HbA_{1C} was 7.9%. After 26 weeks, HbA_{1C} was reduced 0.2 to 7.6% in the insulin detemir group ($P = 0.004$) and 0.4 to 7.5% in the NPH group ($P = 0.0001$). Self-measured blood glucose profiles and reductions in fasting plasma glucose were similar in the two groups. Within-subject variation in fasting self-monitored blood glucose was lower with insulin detemir ($P = 0.021$). Patients treated with insulin detemir also experienced less weight gain (1 vs 1.8 kg; $P = 0.017$). Hypoglycemia risk was similar in the two groups.[42]

Contraindications

Insulin detemir is contraindicated in patients hypersensitive to insulin detemir or any of the product excipients.[1]

Warnings and Precautions

The warnings and precautions for insulin detemir are similar to those associated with other longacting insulin formulations (e.g., NPH insulin, insulin glargine) and include hypoglycemia, hypokalemia, lipodystrophy, hypersensitivity, renal impairment, and hepatic impairment.[1,18] (Table 2) compares the contraindications, warnings, and precautions for insulin detemir and insulin glargine.

Insulin detemir is not to be used in insulin infusion pumps.[1] Insulin detemir is not intended for IV or intramuscular (IM) administration. IV administration of the usual dose could result in severe hypoglycemia. Absorption following IM administration is faster and more extensive than absorption after subQ administration.[1]

Table 2. Contraindications, Warnings, and Precautions of Insulin Detemir and Insulin Glargine[1,18]

	Insulin Detemir	*Insulin Glargine*
Contraindications		
Hypersensitivity	X	X
Warnings and Precautions		
Hypoglycemia	X	X
Change in insulins or oral antidiabetic agents	X	X
Intravenous (IV) administration	X	X
Dilution or mixing	X	X
Renal impairment	X	X
Hepatic impairment	X	X
Injection site reactions/lipodystrophy	X	X
Allergic reactions	X	X
Intercurrent conditions[a]	X	X
FDA pregnancy category	C	C
Breastfeeding mothers	Caution	Caution

[a]Illness, emotional disturbances, or other stresses

Insulin detemir should not be diluted or mixed with any other insulin preparations.[1]

Although pharmacokinetic and clinical studies in children and adolescents have been reported, insulin detemir has not yet been approved for use in this patient population. In contrast, insulin glargine is approved for use in children 6 years of age and older with type 1 diabetes.[18]

Insulin detemir is in Pregnancy Category C. In animal studies, insulin detemir has produced similar effects as human insulin with regard to embryotoxicity and teratogenicity. At doses producing exposure at much higher levels than is seen with typical human doses, effects included visceral anomalies, and dose-related gallbladder abnormalities.[1]

Adverse Reactions

Reactions seen with insulin detemir were similar to those typically observed with other insulin products and included hypoglycemia, allergic reactions, lipodystrophy, pruritus, rash, and weight gain. Hypoglycemia is the most common adverse reaction associated with insulin detemir therapy. Severe hypoglycemia occurred at an incidence similar to that observed with NPH insulin. Mild injection site reactions occurred more frequently with insulin detemir than with NPH insulin, but usually resolved within a few days to a few weeks. Patients treated with insulin detemir experienced less weight gain than those treated with NPH insulin.[1]

Drug Interactions

Protein-binding drug interactions appear unlikely; *in vitro* and *in vivo* protein binding studies have not demonstrated clinically important interactions between insulin detemir and fatty acids or other protein-bound drugs.[1,43] Tolbutamide and glyburide do not compete with insulin detemir for albumin binding at therapeutic concentrations. At high concentrations, aspirin and ibuprofen decrease the affinity of insulin detemir for albumin; however, this interaction is unlikely to occur at the concentrations used in most patients.[43]

Dosage adjustment and close monitoring are also recommended with medications that may reduce or increase the blood glucose-lowering effect of insulin.[1]

Insulin detemir should not be mixed with any other insulin preparations because, the pharmacodynamic profile of one or both insulin components may be altered. Mixing insulin detemir with insulin aspart resulted in a 40% reduction in AUC and peak concentration for insulin aspart, compared with separate injections when the ratio of insulin aspart to insulin detemir was less than 50%.[1]

Recommended Monitoring

Blood glucose should be closely monitored in all patients receiving any form of insulin therapy, along with periodic measurements of the HbA_{1C}.

Dosing

Insulin detemir should be administered once or twice daily as a subQ injection in the thigh, abdominal wall, or upper arm. Injection sites should be rotated within the same region. If administered once daily, it should be administered with the

evening meal or at bedtime. For patients requiring twice-daily administration for blood glucose control, the evening dose of insulin detemir may be administered with the evening meal, at bedtime, or 12 hours after the morning dose.[1]

Patients being switched from other intermediate or long-acting insulin preparations to once- or twice-daily insulin detemir can be switched on a unit-to-unit basis; however, dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia. In some patients with type 2 diabetes, more insulin detemir may be required than NPH insulin.[1]

Insulin-naïve patients with type 2 diabetes and are inadequately controlled on oral diabetic medications may be started on an insulin detemir dosage of 0.1 to 0.2 units/kg once daily in the evening or 10 units once or twice daily, with the dosage adjusted to achieve glycemic targets.[1]

Product Availability

Insulin detemir received Food and Drug Administration (FDA) approval in June 2005. It is available as a clear, colorless, aqueous, neutral sterile solution. Each milliliter of solution contains insulin detemir 100 units (14.2 mg/mL), zinc 65.4 mcg, m-cresol 2.06 mg, mannitol 30 mg, phenol 1.8 mg, disodium phosphate dihydrate 0.89 mg, sodium chloride 1.17 mg, and water for injection. Hydrochloric acid and/or sodium phosphate may have been added to adjust pH to approximately 7.4.[1]

Insulin detemir is supplied in 10 mL vials, 3 mL *PenFill* cartridges, *InnoLet* packages, and *FlexPen* packages. Unused insulin detemir should be stored between 2° and 8° C (36° to 46° F), and protected from freezing. After initial use, product in vials should ideally be refrigerated. If refrigeration is not possible, the in-use vial can be kept at room temperature, below 30° C (86° F), for up to 42 days. After initial use, the cartridge and prefilled syringe dosages may be used for up to 42 days if kept at room temperature, below 30° C (86° F). In-use cartridges and prefilled syringes must not be stored in the refrigerator and must not be stored with the needle in place.[1]

The available dosage forms for insulin detemir, insulin glargine, and NPH insulin are summarized (in Table 3); storage conditions and compatibility are summarized (in Table 4).

Conclusion

Insulin detemir is a long-acting insulin formulation that will provide an alternative to NPH insulin and insulin glargine. Compared with NPH insulin, insulin detemir has a flat activity profile and does not produce peak insulin concentrations like those observed with NPH insulin. Comparisons with insulin glargine are not available.

Table 3. Available Dosage Forms of Insulin Detemir, Insulin Glargine, and NPH Insulin[1,18,19]

Insulin	Vials	Cartridges	Prefilled syringes
Insulin detemir	10 mL	3 mL PenFill	3 mL InnoLet 3 mL FlexPen
Insulin glargine	10 mL	3 mL OptiClick	
NPH insulin	10 mL	3 mL NovoPen	3 mL InnoLet 3 mL Humulin N Pen

Table 4. Storage Conditions and Expiration Dating for Insulin Detemir, Insulin Glargine, and NPH Insulin[1,18,19]

Insulin	Not in-use (unopened) refrigerated	Not in-use (unopened) room temperature	In-use (opened)	Compatible mixed with
Insulin detemir				
10 mL vial	Until expiration date	42 days refrigerated or room temperature	42 days	Do not mix
Cartridges and prefilled syringes/ pens	Until expiration date	42 days	42 days (do not refrigerate)	–
Insulin glargine				
10 mL vial refrigerated or room temperature	Until expiration date	28 days	28 days	Do not mix
Cartridges	Until expiration date	28 days	28 days (do not refrigerate)	–
NPH insulin				
10 mL vial	Until expiration date	30 days	30 days refrigerated or room temperature	Regular insulin, insulin glulisine, insulin glulisine, insulin lispro
Cartridges	Until expiration date	–	14 days (do not refrigerate)	–

However, it appears that insulin detemir produces a similar type of flat activity profile as insulin glargine. Insulin detemir has a shorter duration of action than insulin glargine and more frequently requires twice-daily administration like NPH insulin. It is available in a number of dosage forms, but offers no clear advantages over insulin glargine.

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